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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,248	DAVIS, PETER D.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-45* is/are pending in the application.

4a) Of the above claim(s) *10,14 and 37-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-13 and 18-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 and newly added claims 18-45 are currently pending in the instant application. Claims 15-17 were cancelled in the amendment filed 2 January 2004, claims 1-9, 11-13 and 18-36 are rejected and claims 10, 14 and 37-45 are withdrawn from consideration as being for a non-elected subject matter.

Election/Restrictions

Newly submitted claims 37-45 and amended claims 10 and 14 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the inventions of claims 10, 14 and 37-45 are methods of treating diseases, whereas the claim 1-9, 11-13 and 15-36 are claims to compounds and compositions. These inventions are independent or distinct since the methods of treating a disease involving neovascularisation can be performed by various other compounds or compositions such as combretastatin A-4.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 10, 14 and 37-45 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Amendment and Arguments

Applicants amendment filed 2 January 2004 has overcome the objection of claims 9 and 13 and cancelled claims 15-17 as being substantial duplicates. The amendment of claims 10 and 14 has overcome the 35 USC 112 second paragraph

rejection, however, the amendment has amended the claims to an invention that was not originally present in the claims, and the claims are therefore withdrawn from consideration as being for non-elected subject matter.

In regards to the 35 USC 103(a) rejections, applicant's amendments and arguments filed 2 January 2004 have been fully considered but they are not persuasive. It is noted that the test result pages have not been considered for the determination of unobvious results since the data is not presented in the form of a signed and dated 37 CFR 1.132 declaration.

Applicant argues that the patentability over the cited art is set out on pages 2 and 3 of the specification. Furthermore applicant states that there is no formula in the Woods prior art which having a hydroxy group at the 3' position, that the woods data shows that there is a considerable loss in potency when the 3' hydroxy is eliminated and the 4' methoxy is replaced and that for claims 5-9 the mechanism of the conversion of phosphate prodrugs into active agents relies on an efficient enzymatic cleavage of the phosphate group.

Pages 2 and 3 of the instant specification state that the removal of the 4' methoxy group would considerably reduce the biological activity and that it is unexpected that replacing the 4'methoxy would result in compounds with similar potency. However, it is noted that Woods et al discloses that the 3' hydroxyl group has a relatively small effect on binding to tubulin and that the 4' methoxy group can be replaced with small hydrophobic groups while still retaining significant activity against tubulin.

While there is no formula in the Woods prior art having a hydroxy group at the 3' position (which would be a 102(b) if present) the Woods prior art document does disclose that the 3' OH group is optional and the Woods prior art document does disclose that the cis-methyl and ethyl-stilbenes, wherein the 4' methoxy group has been replaced with methyl or ethyl, does show strong interaction with tubulin and can inhibit assembly of microtubules, cause disruption of intracellular microtubular structure and inhibit colchicines binding to tubulin and are cytotoxic to cultured cells (page 709).

Applicants argument in regards to the conversions of the phosphate prodrugs is an argument based on limitations that are not found in the claims. Applicants prodrug claims do not have the limitation as to how the prodrug is cleaved in vivo. The claims are only drawn to prodrugs which are obvious over the prior art of record.

Therefore, the 35 USC 103(a) rejections of the claims 1-9 and 11-13 are maintained and newly added claims 18-36 are also rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. (reference AT on form 1449).

Applicant's instant claims 1-4 are drawn towards a cis-stilbene of formula (I) (claim 1) wherein R1, R2, R3 can be methyl (claim 2), R5 is hydrogen and R4 is alkyl or halo (claim 3). Claim 4 is drawn to the specific compound (Z) –1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane.

Determining the scope and contents of the prior art

The prior art reference of Woods et al. discloses Combretastatin A-4, figure 1, page 705, which interacts with tubulin with resultant disruption of microtubular function. Page 709 of Woods et al. discloses that the 4'methoxy and 3'hydroxy groups of combretastatin A-4 are not essential for the interaction with tubulin. Furthermore, page 710 of Woods et al. discloses Figure 8 which shows that small alkyl groups at a position equivalent to applicant's R4 do not adversely affect activity of the compound and methoxy is not essential at this position. Page 710 discloses that the interaction with tubulin is tolerant of the replacement of the 4'-methoxy by methyl or ethyl, and also, (e) of page 710 discloses that the replacement of the 4'methoxy group of combretastatin A-4 can be replaced with small hydrophobic groups while still retaining significant activity against tubulin

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art reference and the claims at issue is that in the position equivalent to applicant's R4 substituent, the prior art reference contains a methoxy group, which is not a variable included in applicant's instant claims.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art at the time of the invention to prepare compounds of applicant's instant claim 1, which have vascular damaging activity, including compounds of applicants instant claim 1 wherein R1, R2, and R3 are methyl, R4 is alkyl and R5 is hydrogen when faced with combretastatin A4 in the prior art reference of Woods et al. The motivation is provided in the prior art reference by the disclosure that small alkyl groups at the 4' position do not adversely affect activity of the compound, that methoxy is not essential at the 4' position, that the interaction with tubulin is tolerant of the replacement of the 4'methoxy with methyl or ethyl and that the 4'methoxy can be replaced with small hydrophobic groups while still retaining significant activity against tubulin. The disclosure by Woods et al. that the 4'metoxy group is not necessary and that the replacement of the 4'-methoxy by a small alkyl group or small hydrophobic group would not adversely affect the activity of the compound would motivate someone of ordinary skill in the art to prepare compounds as instantly claimed by applicant in order to have more compounds which are useful for the disruption of microtubular function and for the treatment of tumors.

Claims 5-9, 11-13 and 18-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. as applied to claims 1-4 above, and further in view of WO 92/16486 or WO 99/35150.

Applicants instant claims 5-9, 11-13 and 18-36 are drawn towards prodrugs of the compound of formula (I), specifically phosphate esters of the compound of formula (I) and compositions of the compound of formula (I)

Determining the scope and contents of the prior art

WO/92/16486 discloses compounds which have greater aqueous solubility than Combretastatin A4 and exhibit greater stability, which are prodrugs such as the compound of formula (I) (page 2) wherein Y is a phosphate or a phosphate derivative, the prodrug of the phosphate derivative is particulary preferred (page 3). These compounds can be dissolved in a phosphate buffered saline (page 20) for the preparation of a pharmaceutical formulation of the compound.

WO 99/35150 discloses combretastatin A4 prodrugs, of which phosphate salts are the most stable and suitable (page 6). Page 7 discloses phosphate ester prodrugs which are water soluble. These compounds can be added to a sterile vehicle such as water to be administered as a pharmaceutical composition (page 36).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art of WO 92/16486 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

The difference between the prior art of WO 99/35150 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art to prepare phosphate ester prodrugs of the compound as found in applicants instant claim 1 and to prepare pharmaceutical compositions when faced with the prior art reference of Woods at al. and one of WO 92/16486 or WO 99/35150 since Woods et al. discloses that the 4'methoxy of Combretastatin A-4 can be replaced by a small alkyl group or a small hydrophobic group without causing an adverse reaction in activity and Wo 92/16486 or WO 99/35150 disclose the phosphate ester prodrugs of Combretastatin A4 and disclose that these phosphate esters have improved aqueous solubility and characteristics for use as a prodrug in pharmaceutical formulations. One of ordinary skill in the art would be motivated to prepare prodrugs of the formula as instantly claimed by applicant and to prepare pharmaceutical compositions by the prior art references to prepare other useful compounds which interact with tubulin and are useful in the treatment of cancer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (571-272-0699.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier number for accessing the facsimile machine is (703) 872-9306

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